REMARKS

Claims 32 - 36 and 55 are in this application; no claims having been cancelled in this response; and Claims 37 - 54 and 56 having been previously withdrawn.

Elections of Species:

In the Office Action mailed November 3, 2005, the Examiner acknowledged Applicants' response to the Restriction Requirement dated May 15, 2005, with the Applicants having elected Group II for examination and further elect the species that is "a compound that is nicotinic acid as a compound of Formula III," and the species that is "a compound that is nicotinamide of formula V" as a compound having vitamin PP activity. (Underline added).

However, in the Office Action of November 3, 2005, the Examiner alleges that "[b]ecause two species have not been elected, as proposed, this election is nonresponsive." See page 2 of Office Action. Applicants respectfully disagree with the Examiner's contention that the election is not responsive, as Applicants note that nicotinic acid and nicotinamide are clearly distinct chemical species as shown, for example, in the entries in Hawley's Condensed Chemical Dictionary. For the Examiner's review, a copy of page 818 of the Chemical Dictionary showing the entries of both compounds, is enclosed. Accordingly, in the response of August 17, 2005, Applicants assert that the election of the species nicotinic acid and nicotinamide constitute the election of two distinct chemical species and therefore, the election was responsive to the Restriction Requirement.

Furthermore, on page 2 of the Office Action, the Examiner also alleges that Applicants failed to re-affirm the election of species, as requested in the previous Office Action. However, Applicants note that on page 33 (second paragraph, line 2) of Applicants' response dated August 17, 2005, Applicants clearly stated that "Applicants hereby affirm again" the species nicotinamide and also elect nicotinic acid for examination.

According to the Examiner, "[i]n the interests of advancing prosecution," the Examiner notes that the Office Action dated November 3, 2005 would be "based on the election of species made by Applicants on February 6, 2003" and that "the subject matter now under consideration are those methods of reducing side effects or neutralizing side effects of a cancerostatic or immunosuppressive agent wherein nicotinamide or nicotinic acid is the compound administered, claims 32-36 and 55." See bottom of page 2 of the Office Action.

In the interest of advancing prosecution on the merits, Applicants affirm that the species elected for examination on February 6, 2003 noted by the Examiner above, is the species where:

(1) the compound having vitamin PP activity or prodrug thereof is nicotinamide, a compound [*see* claim 32, for example] of formula V where b is 1, and R^{21}, R^{22}, R^{23}, R^{26}, and R^{27} are all hydrogen; and

(2) the compound of formula I is N-[4-(1-benzoylpiperidin-4-yl)-butyl]-3-(pyridin-3-yl)-acrylamide, a compound [*see* claim 38, for example] where each of $R^{1(i)}$, $R^{2(i)}$, $R^{3(i)}$, and $R^{4(i)}$ is hydrogen, k is 0, $A^{(i)}$ is -CH=CH-, $D^{(i)}$ is $-(CH_2)_4-$, E is piperidin-4-yl, and G is 1-benzoyl.

Applicants concurs with the Examiner's statement that the matter now under consideration are those methods of reducing side effects or neutralizing side effects of a cancerostatic or immunosuppressive agent wherein nicotinamide or nicotinic acid is the compound administered. Applicants also affirm the examiner's statement that claims 32-36 and 55 are now under consideration.

List of Related Patent Applications:

On page 3 of the Office Action, the Examiner requested a "complete list of co-pending and related applications, regardless of the stage of prosecution, for any of the ten named inventors that relate to the present method of use." Accordingly, listed in the Tables below are the co-pending and related applications. Neither the corresponding priority applications nor the respective PCT applications are included in this list.

Antitumor I - filed June 20, 1997
New pyridyl alkane acid amides as cytostatics and immunosuppressives

Country	Application/Patent No.	Status
European patent	EP 0 934 309	granted
US	US 6,444,823	granted
US (continuation-in-part)	US 10/208,656	under examination
Japan	JP 1998/502316	under examination
South Africa	ZA 97/5439	granted

Antitumor II - filed June 20, 1997
Pyridyl alkene- and pyridyl alkyne-acid amides as cytostatics and immunosuppressive

Country	Application/Patent No.	Status
European patent	EP 0 923 570	granted
US	US 10/213,952	under examination
Japan	JP 2000/5169913	under examination
Australia	AU 736206	granted
Brazil	BR 97/09823	under examination
Canada	CA 2,257,448	under examination

Country	Application/Patent No.	Status
China	CN 156845	granted
China (div)	CN 2004/10032586.6	lapsed
Czech Republic	CZ 291791	granted
Hong Kong	HK 1021974	registered
Hungary	HU 99/03766	under examination
Israel	IL 127352	granted
Korea (South)	KR 478 405	granted
Mexico	MX 9225130	granted
Russia	RU 2200734	granted
Turkey	TR 98/02651	under examination
South Africa	ZA 97/5437	granted

Antitumor III - filed June 20, 1997
Use of pyridyl alkane, pyridyl alkene and/or pyridyl alkyne acids amides in the treatment of tumors or for immunosuppression

Country	Application/Patent No.	Status
European patent	EP 0 912 176	granted
US	US 6,451,816	granted
US (continuation-in-part)	US 10/208,253	under examination
Japan	JP 2000/512652	under examination
South Africa	ZA 97/5443	granted

Antitumor IV - filed December 16, 1998
New piperazinyl-substituted pyridylalkane, alkene and alkyne carboxamides

Country	Application/Patent No.	Status
European patent	EP 1 060 163	granted
US	US 6,903,118	granted
Japan	JP 2002/538990	under examination
South Africa	ZA 98/11235	granted

Antitumor V - filed December 16, 1998
New piperazinyl-substituted pyridylalkane, alkene and alkyne carboxamides

Country	Application/Patent No.	Status
European patent	EP 1 044 197	granted
US	US 6,593,344	granted
Japan	JP 2003/538987	under examination
South Africa	ZA 98/11241	granted

Antitumor VI - filed December 16, 1998
Cyclic imide-substituted pyridylalkane, alkene and alkyne carboxamides useful as cytostatic and immunosuppressive agents

Country	Application/Patent No.	Status
European patent	EP 1 042 315	granted
US	US 09/595,218	under examination
Japan	JP 2002/508367	under examination
South Africa	ZA 98/11231	granted

Antitumor VII - filed December 16, 1998
Aryl-substituted pyridylalkane, alkene, and alkyne carboxamides useful as cytostatic and immunosuppressive agents

Country	Application/Patent No.	Status
European patent	EP 1 042 291	granted
US	US 09/596,086	under examination
Japan	JP 2002/508357	under examination
South Africa	ZA 98/11240	granted

Antitumor VIII - filed April 21, 1999
Use of Vitamin PP Compounds

Country	Application/Patent No.	Status
European patent	EP 1 079 832	granted
US	US 09/693,558	under examination
Japan	JP 2002/512190	examination to be requested by April 2006

Antitumor IX - filed February 28, 2000
Inhibitor of cellular niacinamide mononucleotide formation

Country	Application/Patent No.	Status
European patent	EP 1 154 998	under examination
US	US 6,506,572	granted
Japan	JP 2002/537380	examination to be requested by February 2007

Antitumor X - filed March 24, 2003
Use of Pyridyl Amides As Inhibitors of Angiogenesis

Country	Application/Patent No.	Status
European patent	EP 1 487 444	under examination
US	US 10/509,362	under examination
Japan	JP 2003/577882	examination to be requested by March 2006

Abstract of the Disclosure:

The Examiner objected to the abstract of the disclosure as not directed to the subject matter presently under consideration. As noted above, the abstract has been amended to recite the subject matter under consideration. Withdrawal of the objection is requested.

Rejection Under 35 U.S.C. 112, First Paragraph:

Applicants note with appreciation the Examiner's withdrawal of the rejection of claim 32-36 and 55 under 35 U.S.C. 112, first paragraph, as it applies to the administration of nicotinamide or nicotinic acid.

Rejection Under 35 U.S.C. 112, Second Paragraph:

The Examiner rejected claims 32-36 and 55 under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which Applicants regard as the invention. In particular, the Examiner alleges that the recitation "or a prodrug thereof" in claims 32, 33, 35, 36 and 55 lacks clarity with respect to the compounds Applicants contemplate as "prodrugs" and that "the specification provides no guidance as to those compounds that have vitamin PP activity and may be administered in methods for reducing side effects of a cancerostatic or immunosuppressive agents" and that "the metes and bounds of the term "prodrug" cannot be precisely determined in this case."

It is well know in the art of pharmaceutical chemistry and pharmaceutical sciences, in general, that the term "prodrug" means a compound formed by chemical modification of a biologically active compound that will liberate the active compound *in vivo* by enzymatic or hydrolytic cleavage. See, for example, Remington: The Science and Practice of Pharmacy, Alfonso R. Gennaro, 20th Edition, Philadelphia, PA. A copy of the relevant pages of this reference is attached for the Examiner's review. In one well established example of a prodrug, for example, a compound that is a carboxylic acid, such as nicotinic acid, may be derivatized to the corresponding ester to form the prodrug, and the prodrug may be administered as the ester which is then converted under hydrolytic condition *in vivo* to form

the carboxylic acid. For such esters as is well known in the art, such ester derivatives may include acetates, propionates, succinates, and esters of amino acids, and the like.

In addition, as exemplified on page 52 and also throughout the specification, examples of such ester derivatives of nicotinic acid include the compound represented by Formula (IV) (page 52), wherein R^{25} is selected from "monovalent, straight chained or branched, primary, secondary or tertiary C_1-C_{10}-alkanols etc ..." See page 53 of the specification. Accordingly, Applicants respectfully assert that the term "prodrug" is well known in the art and is clearly exemplified in the present specification as filed and the term "prodrug" as used herein is not indefinite.

Withdrawal of the 35 U.S.C. 112, second paragraph, rejection is respectfully requested.

Rejection Under 35 U.S.C. 102(a):

In view of the claims under examination, Applicants note with appreciation the Examiner's withdrawal of the rejection of claims 32-38 under 35 U.S.C. 102(a) as being anticipated by Budihardjo et al.

Rejection Under 35 U.S.C. 102(b):

Claims 32-36 and 55 are rejected under 35 U.S.C. 102(b) as being anticipated by Nurmukhembetov *et al.*, Kardiologia, (abstract). According to the Examiner, "Nurmukhembetov teaches the administration of the compound niacinamide having PP vitamin activity to reduce side effects relating to cardiac contractility as a result of an injection of the cancerostatic agent adriblastin."

Applicants respectfully traverse the rejection of claims 32-36 and 55 over Nurmukhembetov *et al.*

As summarized in the abstract of Nurmukhembetov, Nurmukhembetov simply discloses the pretreatment of nicotinamide 3 days prior to intraperitoneal injection of adriblastin for the prevention of cardiac contractility in adriblastin-treated rats. Applicants respectfully assert that Nurmukhembetov does not disclose nor suggest the subject matter of independent claim 32 of the present application, which is a method for reducing side effects or neutralizing the side effects of a cancerostatic or immunosuppressive agent by the prophylactic or therapeutic administration of a compound having vitamin PP activity or a prodrug thereof. Applicants submit that a method for the prevention of cardiac contractility in adriblastin-treated rats does not anticipate nor suggest the method for reducing side effects or neutralizing the side effects of a cancerostatic or immunosuppressive agent as recited in claim 32 of the present application.

Withdrawal of the rejection of claims 32-36 and 55 under 35 U.S.C. 102(b) over Nurmukhembetov is respectfully requested.

Claims 32-36 and 55 are rejected under 35 U.S.C. 102(b) as being anticipated by Giri *et al.* According to the Examiner, Giri *et al* teaches the administration of the compound niacin having PP vitamin activity "to reduce the chemically-induced side effect interstitial pulmonary fibrosis that results from administration of the cancerostatic agent bleomycin."

Applicants respectfully disagree with the Examiner's characterization of the disclosure of Giri *et al* and the conclusion drawn therefrom, as it relates to the present invention. Giri *et al* teach that the combined treatment with taurine in drinking water and niacin IP daily significantly decreased the BO-induced increases in lung MDAE and calcium content etc ... and completely ameliorated the BL-induced increases in the lung collagen accumulation. Applicants respectfully assert that Giri *et al* teach the administration of a combination of products including the compound taurine, and do not teach nor even suggest the method for reducing side effects or neutralizing the side effects of a cancerostatic or immunosuppressive agent comprising administering a compound having vitamin PP activity or a prodrug thereof, as recited in claim 32 of the present application.

Withdrawal of the rejection of claims 32-36 and 55 under 35 U.S.C. 102(b) over Giri *et al* is respectfully requested.

Claims 32-36 and 55 are rejected under 35 U.S.C. 102(b) as being anticipated by Stevens *et al.* According to the Examiner, "Stevens teaches the administration of the compound having PP vitamin activity, nicotinic acid, to neutralize a dermatologic side effect, a rash, that was exacerbated by administration of the cancerostatic agent 5-fluorouracil. Pellagra is presented as a chemically-induced side effect secondary to 5-fluorouracil."

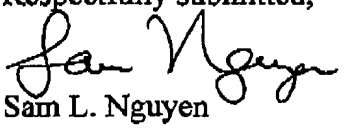
Applicants respectfully disagree with the Examiner's characterization of Stevens *et al* as a disclosure that may relate to the claims of the present application. Stevens *et al* offers the observations that "the typical changes of pellagra ... rash and an associated acute deterioration in cerebral function were exacerbated by treatment with 5-fluorouracil" and "reasons for possible under diagnosis of pellagra in association with malignant disease" and that "[t]he importance of considering nicotinic-acid deficiency in patients with malignant disease has not been emphasized in the literature." (Underline added). Accordingly, Stevens *et al* do not teach nor even suggest the method for reducing side effects or neutralizing the side effects of a cancerostatic or immunosuppressive agent comprising administering a compound having vitamin PP activity or a prodrug thereof, as recited in claim 32 of the present application.

Withdrawal of the rejection of claims 32-36 and 55 under 35 U.S.C. 102(b) over Stevens *et al* is respectfully requested.

Claims 32-36 and 55 pending in this application are believed to be in *prima facie* condition for allowance, and an early action to that effect is respectfully solicited.

Allowance of the claim 32-36 and 55 is respectfully requested. Please direct any calls in connection with this application to the undersigned at the number provided below.

Respectfully submitted,



Sam L. Nguyen
Attorney for Applicants
Reg. No. 52,496

Customer No.: 25213
Heller Ehrman LLP
275 Middlefield Road
Menlo Park, CA 94025-3506
(650) 324-7028
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orifice, as shown in Figure 47-9.[14] The membrane will allow free diffusion of water but not drug. When the tablet is exposed to water or any fluid in the body, water will flow into the tablet because of osmotic pressure difference, and the volume flow rate, dV/dt, of water into the tablet is

$$dV/dt = (kA/h)(\Delta\pi - \Delta P) \quad (34)$$

where k, A, and h are the membrane permeability, area, and thickness, respectively, $\Delta\pi$ is the osmotic pressure difference, and ΔP is the hydrostatic pressure difference. If the orifice is sufficiently large, the hydrostatic pressure difference is small compared with the osmotic pressure difference, and Equation 34 becomes

$$dV/dt = (kA/h)\Delta\pi \quad (35)$$

Thus, the volume flow rate of water into the tablet is determined by permeability, area, and thickness of the membrane. The drug will be pumped out of the tablet through the orifice at a controlled rate, dM/dt, equal to the volume flow rate of water into the tablet multiplied by the drug concentration, C_s:

$$dM/dt = (dV/dt)C_s \quad (36)$$

The release rate will be constant until the concentration of drug inside the tablet falls below saturation.

Several modifications of the osmotic pressure-controlled drug-delivery system have been developed. A layer of bioerodible polymer can be applied to the external surface of the semipermeable membrane. A system consists of two compartments separated by a movable partition, as shown in Figure 47-10.[15] For a system that does not have an orifice, hydraulic pressure is built up inside as the GI fluid is imbibed, until the wall ruptures and the contents are released to the environment.

The advantage of the osmotic system is that it requires only osmotic pressure to be effective and is essentially independent of the environment. The drug release rate can be predetermined precisely regardless of pH change through the GI tract. Some materials used as the semipermeable membrane include polyvinyl alcohol, polyurethane, cellulose acetate, ethylcellulose, and polyvinyl chloride. Drugs that have demonstrated successful release rates from an osmotic system *in vivo* after oral dosing are potassium chloride and acetazolamide.

Ion-Exchange Resins

Ion-exchange resins are water-insoluble, cross-linked polymers containing salt-forming groups in repeating positions on the polymer chain. Drug is bound to the resin by repeated exposure of the resin to the drug in a chromatographic column or by prolonged contact of the resin with the drug solution. The drug-resin then is washed to remove contaminating ions and dried to form particles or beads. Drug release from the drug-resin complex depends on the ionic environment, ie, pH and electrolyte concentration, within the GI tract as well as properties of the resin.

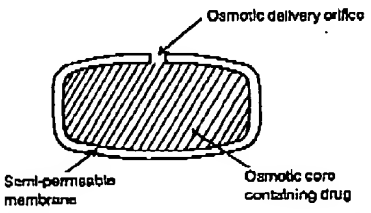


Figure 47-9. Schematic diagram of an osmotic tablet. (Reproduced with permission.[14])

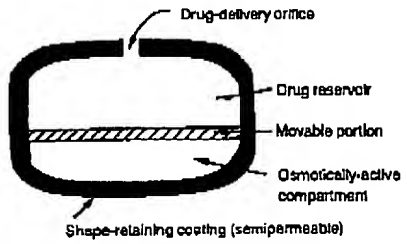


Figure 47-10. Osmotic pressure-controlled drug-delivery system with two compartments separated by a movable partition. (Reproduced with permission.[15])

Drug molecules attached to the resin are released by exchanging with appropriately charged ions in the GI tract followed by diffusion of the free drug molecule out of the resin. The rate of diffusion is controlled by the area of diffusion, diffusional path length, and extent of cross-linking in the resin. A modification of the release rate can be made by coating the drug-resin complex. Further improvement of this ion-exchange type drug-delivery system is called the Penn Kinetic system. In this system, the drug-containing resin granules first are treated with an impregnating polymer such as PEG 4000 to retard the rate of swelling in water and further coated with a water-insoluble polymer, such as ethylcellulose, to serve as a rate-limiting barrier to control drug release.

Most ion-exchange resins currently employed in sustained-release products contain sulfonic acid groups that exchange cationic drugs such as those with an amine functionality. Examples of some of these drugs are amphetamine, phenyl t-butylamine (phentermine), phenyltoloxamine, and hydrocodone, as shown in Table 47-6.

Prodrugs

A prodrug is a compound formed by chemical modification of a biologically active compound that will liberate the active compound *in vivo* by enzymatic or hydrolytic cleavage. The primary purpose of employing a prodrug for oral administration is to increase intestinal absorption or to reduce local side effects, such as GI irritation by aspirin. On this basis, one generally does not classify a prodrug as a controlled-release dosage form. However, the ability to bioreversibly modify the physicochemical properties of a drug allows better intestinal transport properties and hence influences the drug blood level versus time profile. Thus, prodrugs can be used to increase the strategies for controlled release and, in a limited sense, can be controlling in their own right.

As an example of the use of a prodrug as a controlled mechanism, consider a water-soluble drug that is modified to a water-insoluble prodrug. The prodrug will have a slower dissolution rate in an aqueous medium than the parent drug, and thus the appearance of the parent drug in plasma will be slowed. This is observed with theophylline and its prodrug, 7,7'-succinylditheophylline. Alternatively, a water-soluble prodrug of a water-insoluble parent drug can be made to be a substrate for enzymes in the brush border region of the mi-

Table 47-6. Ion-Exchange Products

PRODUCTS	ACTIVE INGREDIENT(S)	MANUFACTURER
Biphetamine capsules	Amphetamine, dextroamphetamine	Pennwalt
Tussionex capsules, tablets, suspensions	Hydrocodone, chlorpheniramine	Pennwalt
Ionamin capsules	Phentermine	Pennwalt

Hawley's Condensed Chemical Dictionary

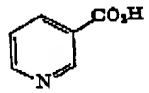
ELEVENTH EDITION

Revised by

N. Irving Sax
and
Richard J. Lewis, Sr.

VNR VAN NOSTRAND REINHOLD COMPANY
New York 1987

niacin. (nicotinic acid; pyridine-3-carboxylic acid). CAS: 59-67-6.



The antipellagra vitamin, essential to many animals for growth and health. In man, niacin is believed necessary along with other vitamins for the prevention and cure of pellagra. It functions in protein and carbohydrate metabolism. As a component of two important enzymes, coenzyme I and coenzyme II, it functions in glycolysis and tissue respiration.

Properties: Colorless needles, odorless, mp 236C, sublimes above melting point, sour taste, soluble in water and alcohol, insoluble in most lipid solvents, quite stable to heat and oxidation, d 1.473, a vasodilator in high concentration.

Units: Amounts of niacin are expressed in milligrams.

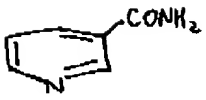
Sources: Food sources, meat, fish, milk, whole grains, yeast. Commercial sources: synthetic niacin is made by oxidation of nicotine, quinoline, or 2-methyl-5-ethylpyridine (from ammonia and formaldehyde or acetaldehyde).

Grade: NF, FCC, blended with soy flour (animal feeds).

Use: Medicine (cholesterol-lowering agent), nutrition, feeds, enriched flours, dietary supplement.

See also niacinamide.

niacinamide. (nicotinamide; nicotinic acid amide). CAS: 98-92-0. $C_5N_4NCONH_2$. Same biological function as niacin.



Properties: Colorless needles, mp 129C, d 1.40. Soluble in water, ethanol, and glycerol; bitter taste.

Sources: Synthetic made by conversion of niacin to the amide.

Grade: USP, FCC. Also commercially available as the hydrochloride.

Use: Medicine, dietary supplement.

niacinamide ascorbate. A complex of ascorbic acid and niacinamide.

Properties: Lemon-yellow powder, odorless or with a very slight odor. May gradually darken upon exposure to air. Soluble in water and alcohol, sparingly soluble in glycerol, practically insoluble in benzene.

Grade: FCC.

Use: Dietary supplement.

"Nial."[155] TM for a nickel-base thermocouple alloy, wherein the negative thermal EMF with reference to pure platinum is obtained by adding manganese, aluminum and silicon. Low percentages of iron, cobalt, zirconium, and magnesium are added to control both the EMF and type of oxide.

Properties: Magnetic, mp 2550F, d 8.47, sp heat at 20C, 0.12 cal/g, tensile strength 83,000 psi.

nialamide. (1-(2-benzylcarbamyl)ethyl-2-isonicotinoylhydrazine). CAS: 51-12-7. $C_5H_4NCO(NH)_2(CH_2)_2CONHCH_2C_6H_5$.

Properties: White, crystalline powder of low solubility in water and good solubility in slightly acid solution. It is stable in crystalline form, suspension, and solution.

Use: In medicine as an antidepressant.

Hazard: Toxic in overdose.

"Nialk."[962] TM for chlorine, caustic soda, caustic potash, carbonate of potash, paradichlorobenzene, and trichloroethylene.

"Niaproof."[214] TM for a water-repellent compound. Substantially a soluble basic aluminum acetate salt.

Use: Source of aluminum ion for water-repellent finishes for textile, paper, and leather products, particularly in processes using wax or soap emulsions.

"Niax."[214] TM for a polyurethane foam preparation packaged in two units: (1) the resin base and (2) the expander or catalyst, said to be composed chiefly of dimethylaminopropionitrile.

nicarbazin. Equimolar complex of 4,4'-dinitrocarbanilide and 2-hydroxy-4,6-dimethylpyrimidine.

Properties: Forms crystals, decomposes at 265–275C, insoluble in water.

Use: Coccidiostat.

niccolite. (arsenical nickel). NiAs.

An ore of nickel.

Properties: Pale copper-red mineral with dark tarnish, metallic luster. Contains 43.9% nickel, soluble in concentrated nitric acid, d 7.3–7.67, hardness 5–5.5.

Hazard: Toxic by inhalation of dust.

"Nichrome."[330] TM for an alloy containing 60% nickel, 24% iron, 16% chromium, 0.1% C.

Use: It is used principally for electric resistance purposes. It also offers good resistance to mine and sea waters and moist sulfurous atmospheres.

nickel. CAS: 7440-02-0. Ni. Metallic element of atomic number 28, group VIII of the Periodic Table, aw 58.70, valences = 2, 4. Five stable isotopes.

Properties: Malleable, silvery metal. Readily fabricated by hot- and cold-working, takes high polish, excellent resistance to corrosion, d 8.908, mp 1455C, bp 2900C, electrical resistivity (20C)